

IN THE SPECIFICATION

The following mark-up scheme is adopted:

Deleted material : ~~Strike through~~;

Inserted material: Underline.

Please revise the specification as follows:

Please amend paragraph starting on page 3, line 30 as follows:

E1
The present invention further provides methods for identifying and designing small molecules that bind to the coactivator binding site using atomic models of nuclear receptors. The method involves modeling test compounds that fit ~~spaeially~~ spatially into a nuclear receptor coactivator binding site of interest using an atomic structural model comprising a nuclear receptor coactivator binding site or portion thereof, screening the test compounds in a biological assay characterized by binding of a test compound to a nuclear receptor coactivator binding site, and identifying a test compound that modulates coactivator binding to the nuclear receptor.

Please amend paragraph starting on page 4, line 19 as follows:

E2
The invention further includes a method for identifying an agonist or antagonist of coactivator binding to a nuclear receptor. The method comprises providing the atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system; modeling compounds which fit ~~spaeially~~ spatially into the nuclear receptor coactivator binding site; and identifying in an assay for nuclear receptor activity a compound that increases or decreases activity of the nuclear receptor through binding the coactivator binding site.

Please amend paragraph starting on page 4, line 31 as follows:

E3
Also provided is a method of identifying a compound that selectively modulates the activity of one type of nuclear receptor compared to other nuclear receptors. The method is exemplified by modeling test compounds that fit ~~spaeially~~ spatially and preferentially into a nuclear receptor coactivator binding site of interest using an atomic structural model of a nuclear receptor coactivator binding site, selecting a compound that interacts with one or more residues of the coactivator binding site unique in the context of that site, and identifying in an assay for coactivator binding activity a compound that selectively binds to the coactivator binding site compared to other nuclear receptors. The unique features involved in receptor-selective coactivator binding can be identified by comparing atomic models of different receptors or isoforms of the same type of receptor.

Please amend paragraph starting on page 10, line 22 as follows:

E4
Compounds that bind to the coactivator binding site of nuclear receptors can be identified by computational modeling and/or screening. For example, coactivator agonists or antagonists can be identified by providing atomic coordinates comprising a nuclear receptor coactivator binding site or portion thereof to a computerized modeling system, modeling them, and identifying compounds that fit ~~spaeially~~ spatially into the coactivator binding site. By a “portion thereof” is intended the atomic coordinates corresponding to a sufficient number of residues or their atoms of the coactivator binding site that interact with a compound capable of binding to the site. This includes receptor residues having an atom within 4.5Å of a bound compound or fragment thereof. For instance, human TR residues V284 Val284, Phe293, Ile302, Leu305 and Leu454 contain side chain atoms that are within 4.5Å, and interact with, hydrophobic residues of a (SEQ ID NO: 1) LxxLL motif of an NR-box 2 coactivator peptide. As another example, an atomic structural model utilized for computational modeling and/or screening of compounds that bind to the coactivator binding site may include a portion of atomic coordinates of amino acid residues corresponding to the site composed of residues of human thyroid receptor selected from Val284, Lys288, Ile302, Lys306, Leu454 and Glu457, or their structural and functional equivalents found in other receptors. Thus, for example, the atomic coordinates provided to the modeling system can contain atoms of the nuclear receptor LBD, part of the LBD such as atoms corresponding to the coactivator binding site or a subset of atoms useful in the modeling and design of compounds that bind to a coactivator binding site.

Please amend paragraph starting on page 11, line 7 as follows:

The atomic coordinates of a compound that fits into the coactivator binding site also can be used for modeling to identify compounds or fragments that bind the site. By “modeling” is intended quantitative and qualitative analysis of molecular structure/function based on atomic structural information and receptor-coactivator agonists/antagonists interaction models. This includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models. Modeling is preferably performed using a computer and may be further optimized using known methods. By “fits ~~spaeially~~ spatially” is intended that the three-dimensional structure of a compound is accommodated geometrically by a cavity or pocket of a nuclear receptor coactivator binding site.

Please amend paragraph starting on page 11, line 17 as follows:

Compounds of particular interest fit ~~spaeially~~ spatially and preferentially into the coactivator binding site. By “fits ~~spaeially~~ spatially and preferentially” is intended that a compound possesses a three-dimensional structure and conformation for selectively interacting with a nuclear receptor coactivator binding site. Compounds that fit ~~spaeially~~ spatially and preferentially into the coactivator

binding site interact with amino acid residues forming the hydrophobic cleft of this site. In particular, the hydrophobic cleft of the coactivator binding site comprises a small cluster of hydrophobic residues. The site also contains polar or charged residues at its periphery. The present invention also includes a method for identifying a compound capable of selectively modulating coactivator binding to different nuclear receptors. The method comprises the steps of modeling test compounds that fit ~~spaeially~~ spatially and preferentially into the coactivator binding site of a nuclear receptor of interest using an atomic structural model of a nuclear receptor, screening the test compounds in a biological assay for nuclear receptor activity characterized by preferential binding of a test compound to the coactivator binding site of a nuclear receptor, and identifying a test compound that selectively modulates the activity of a nuclear receptor. Such receptor-specific compounds are selected that exploit differences between the coactivator binding sites of one type of receptor versus a second type of receptor, such as the differences depicted in Figure 19.

Please amend paragraph starting on page 18, line 16 as follows:

The machine-readable data storage medium can be used for ~~interactive~~ interactive drug design and molecular replacement studies. For example, a data storage material is encoded with a first set of machine-readable data that can be combined with a second set of machine-readable data. For molecular replacement, the first set of data can comprise a Fourier transform of at least a portion of the structural coordinates of the nuclear receptor or portion thereof of interest, and the second data set comprises an X-ray diffraction pattern of the molecule or molecular complex of interest. Using a machine programmed with instructions for using the first and second data sets a portion or all of the structure coordinates corresponding to the second data can be determined.

Please amend paragraph starting on page 36, line 23 as follows:

Several peptides containing GRIP1 NR-box 2 were tested in crystallization trials with the hTR β LBD. The complex of the hTR β LBD with the GRIP1 NR-box 2 peptide 686-KHKILHRLQLDSS-698 (residues 12-24 of SEQ ID NO: 6) produced crystals that were dependent on both the presence and the concentration of the peptide. Without the peptide, the hTR β LBD precipitated immediately. However, nucleation was erratic, but could be overcome through seeding of prepared drops with microcrystals of the hTR β LBD:GRIP1 NR-box 2 peptide complex. Structure of the hTR β LBD:GRIP1 NR-box 2 peptide complex was determined by molecular replacement using the structure of the hTR β LBD determined previously (Wagner *et al.*, *supra*) and refined to a resolution of 3.6Å (Table 1). The refined model consists of residues K211-P254 and V264-D461 of monomer 1 of the hTR β LBD, residues K211-P254 and G261-D461 of monomer 2 of the hTR β LBD, and the GRIP1 NR-box 2 peptides (residues 14-24 of SEQ ID NO: 6) 688-KILHRLQLDSS-698, and (residues 14-22 of SEQ ID NO: 6) 688-KILHRLQLD-696 (Appendix 1). The structure in Appendix 1 consists of: a portion of each of two molecules of hTR β , chain A (SEQ ID NO: 52) and chain B (SEQ

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ID NO: 53); two molecules of T₃, chain J and chain K; and two molecules of GRIP-1 peptide, chain X (SEQ ID NO: 54) and chain Y (SEQ ID NO: 55).

Please amend paragraph starting on page 41, line 36 as follows:

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Ile 689 from the peptide interacts with three receptor residues (Asp 538, Glu 542 and Leu 539). The γ -carboxylate of Glu 542 forms hydrogen bonds to the amides of residues 689 and 690 of the peptide. A water-mediated hydrogen bond network is formed between the imidazole ring of His 377, the γ -carboxylate of Glu 380, and the amide of Tyr 537. Three residues (Glu 380, Leu 536 and Tyr 537) interact with each other through van der Waals contacts and/or hydrogen bonds.

Intriguingly, mutations in each these three residues dramatically increase the transcription activity of unliganded ER α LBD (Eng, *et al.*, *Mol. Cell. Biol.* (1997) 17:4644-4653); Lazennec, *et al.*, *Mol Endocrinol.* (1997) 11:1375-86; White, *et al.*, *EMBO J.* (1997) 16:1427-35). Atomic coordinates of DES-LBD-peptide complex are attached as Appendix 2. The structure in Appendix 2 consists of: a portion of human ER α , chain A (SEQ ID NO: 56) and chain B (SEQ ID NO: 57); two molecules of DES; and two molecules of GRIP-1 NR-box 2 peptide, chain C (SEQ ID NO: 58) and chain D (SEQ ID NO: 59).

Please amend paragraph starting on page 43, line 6 as follows:

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The OHT complex data set was then collected. Starting with one of the monomers of the preliminary low-resolution DES-hER α LBD-NR-box 2 peptide model as the search probe, molecular replacement in AMoRe was used to search for the location of LBD in this crystal form in both P6₁22 and P6₅22. A translation search in P6₅22 yielded the correct solution (R=53.8%, CC=38.2%). In order to reduce model bias, DMMULTI (CCP4, 1994) was then used to project averaged density from the DES complex cell into the OHT complex cell. Using MOLOC, a model of the hER α LBD was built into the resulting density. The model was refined initially in REFMAC and later with the simulated annealing, positional and R-factor refinement protocols in X-PLOR (Brunger, X-PLOR. Version 3.843, New Haven, Connecticut: Yale University, 1996) using a maximum-likelihood target (Adams, *et al.*, *Proc. Natl. Acad. Sci. USA* (1997) 94:5018-23). Anisotropic scaling and a bulk solvent correction were used and all B-factors were refined isotropically. Except for the R_{free} set (a random sampling consisting of 8% of the data set), all data between 41 and 1.9 Å (with no σ cutoff) were included. The final model consisted of residues 306-551, the ligand and 78 waters. According to PROCHECK (CCP4, 1994), 91.6% of all residues in the model were in the core regions of the Ramachandran plot and none were in the disallowed regions. Thus, the structure of the OHT-hER α LBD complex has been refined against data of comparable resolution (1.90 Å) to a crystallographic B-factor of 23.0% (R_{free}=26.2%). Atomic coordinates of OHT-hER α LBD complex are attached as Appendix 3. The structure in Appendix 3 consists of: atomic coordinates for a portion of human ER α (SEQ ID NO: 60) complexed with OHT.